In the past five to ten years, Major Depressive Disorder (MDD) also known as unipolar depression and clinical depression, has baffled psychologists. Numerous studies have been published sharing the results of genetic testing of families with depression. Each study has performed its own genome scan with specific markers to find exactly which chromosomes and regions of DNA (deoxyribonucleic acid) hold the source to major depression, specifically early-onset MDD. Although parts of the results, one or two chromosome regions, have been found to have a statistically significant influence in multiple studies, overall, there has been no clear replication of any one study’s results. In one study by Holmans et al, they found that “no genetic locus makes a large contribution to the overall risk of major depressive disorder, that multiple loci… may contribute to the risk, and that the contribution of some loci may be sex dependent. This is a wonderful summary of their results and points to a couple important factors for the genetic source of MDD. For one, their mention of the sex dependency is a vital factor in genetic risk, and should certainly be studied further. One other thing they mention is the effect of multiple loci. Previously, I mentioned the inconsistency of results in these genome scan studies, and one study suggests the possibility of false positives. However, if we look at the results from all the genome scan studies we see that the results of significant linkage have been replicated at least once on all but one (17p) of the chromosomal regions mentioned. I propose that in fact all of these chromosomal regions with at least one replication (1q, 3q, 4q, 6p, 8p, 11q, 12q, 15q, and 18q) play a statistically significant role in major depression.

Some of these chromosomal regions play a larger role in major depression than others. Chromosome region 1q most likely does not play a role in major depression because the two studies that present it as significant are studies of neuroticism and not major depression. Neuroticism is a related personality trait of MDD, but the chromosomal region 1q was not shown to be significant in any of the MDD genome scans, so it is an unlikely factor in MDD. 3q, 4q, 6p, 8p and 11q all play a minimal role in MDD. Each of these chromosomal regions showed significance in studies of neuroticism and were shown as significant only in one study of MDD. 6p and 8p were only shown as suggestive genetic factors for MDD and play an even smaller role in the genetics of MDD. Another chromosomal region that was shown to be significant for neuroticism was region 12q, but this is more significant for MDD as it was replicated in two genome scans of MDD. Lastly, chromosome regions 15q and 18q have the greatest genetic role in MDD as they were shown to have a significant influence in two or more genome scans of families with MDD. Of these two, 15q plays the largest role as it received strong significance in the three studies in was shown to be significant in and because it was shown to be significant in more studies than 18q. In summary, chromosomal regions 3q, 4q, 6p, 8p, 11q, 12q, 15q, and 18q are all genetic factors in major depression, and they each vary in the severity of their influence.

One study states that “although a classical statistics rule is that the more participants you have in a study, the more accurate your data will be, it appears there is more to the accuracy of genome scans than simply numbers.” Obviously from the inconsistent results of the studies previously mentioned, it is obvious that there is something more. Many of the studies I mentioned had hundreds of families participate and near or above one thousand total participants. With that great of a number of participants, one would assume that all the studies would find the same result. However, this has not been the case. This is evidence that all the chromosomal regions which were replicated in at least one other study play a significant role in MDD. The issue is not accuracy, but simply that there are a large number of influences on major depression. These influences have an impact in these different studies because of the variegation in participants. Participants varied in their comorbid disorders, ancestry, specific age of onset, severity of depression, life events, sex, recurrence of episodes and more.

An explanation for the variety of results in the aforementioned studies is the impact of comorbid disorders on heritability of MDD. Many of the participants and their families had been diagnosed with disorders comorbid with MDD. These included Panic disorder, OCD, other anxiety disorders, and Alcohol or substance abuse and dependence. Also, some studies threw out family members with Bipolar-I and Bipolar-II disorder while others included these participants in their study. This inconsistency could obviously play a role inconsistency in results. I don’t say this to discount the results of any one study. Instead, I say this to explain the differences in prior results and further hypothesize that certain chromosomal regions play a larger or smaller role in MDD depending on that regions role in another comorbid disorder. Comorbid disorders in general present a complicating factor in the analyses of these genome scan results due to the inconsistencies in including participants with certain comorbid disorders. Additionally, certain chromosomal regions suggest a risk for major depression and a risk for the comorbid disorder which further complicates the results and the disorder of MDD. It has been suggested that certain chromosome regions are linked to the comorbid disorders and also have a specific influence in both MDD and the comorbid disorder. I am unsure as to which chromosome regions these would be, but further study should illuminate this issue.

Although not something that I would initially consider, ethnicity could play a role in the variability with MDD genome scan results. Two studies, the GenRED study by Holmans et al and the depression network study by McGuffin et al, looked solely at participants of European descent. Other studies did not discriminate by ancestry, so they may have received a varied result from the Holmans et al study. In fact, many studies have shown differences among ethnicities in their varied reactions to treatment for depression and other depression related factors. This could easily have influenced the genome scan results because while the two aforementioned studies isolated their subjects to Europeans, another study expanded their subject group to include African Americans, Hispanics, and Asians and the other two studies did not even specify the ethnicity of their participants.

This is just one of the factors in methodology that could have had an effect on the final genome scan results. Since genome scans have not been performed solely on subjects of ethnicities outside of European, there is a lack of data to suggest whether or not there is a difference. I would assume since the psychologists who ran two of the studies made an effort to isolate their participants to a specific ethnicity; it seems that these psychologists believe there is a difference in heritability of major depression based on ethnicity. It is then surprising to see that no genome scan has been done with solely participants of non-European ancestry. It would be of great value to the field of psychology for genome scans to be performed with solely African American participants, solely Hispanic participants, and solely Asian participants. Perhaps it was most convenient to study European or Caucasian participants due to accessibility, but this has left a gap in the psychology community’s knowledge of this field. In fact, all the results of the current studies may be drastically different from persons with differing ancestry, and the issue of heritability may need to be readdressed from a different perspective. This is one of the possible causes for the inconsistencies in prior genome scan results, and without fully exploring these issues we cannot fully understand MDD and apply the conclusions of the current genome scan studies to psychology practices.

Another factor in the variegation of results in prior studies of MDD genetic components is the specific age of onset of major depression for the study participants. All participants in the studies I looked at had experienced early-onset major depression, but there is a fine line between adolescent depression and early-onset depression. While I chose to look at early-onset depression, I discovered some data referencing adolescent depression. In one of the studies, it mentions that participants less than 18 years of age were excluded from the study because their cases could be considered adolescent depression. Adolescent depression is a form of depression that has fewer episodes, earlier onset, and shorter duration than MDD; it also has a minimal genetic component, and is often triggered almost solely by life events unlike the other more complex forms of familial depression. If a large number of the cases in a genome scan study were cases of adolescent depression, there would be a huge problem in getting significant data. In the genome scan studies I read, most seemed to be able to find significant results, so cases of adolescent depression may not have been included to severely. However, there was still a large range of ages of onset that could have other implications for the data.

In the studies I looked at, the mean age of onset varied from 17.6 years of age to 28.1 years of age. Most means were more towards the lower end, but there was still a large amount of variability. Those with an earlier age of onset had a higher rate of recurrence of depressive episodes. If there were a large number of participants in the study with a very early age of onset, the data could be skewed to giving data about persons with more severe cases of MDD instead of representing the appropriate spectrum. It is likely that there is some genetic factor that induces major depressive episodes earlier in some persons and later in others. This is evident from the relationship between age of onset and all other aspect of MDD; because age of onset does have a relationship with other factors influencing MDD like the quantity of depressive episodes, it is clear that there is a deeper cause to this specific aspect of major depression. If a genome scan study can be performed with groups of participants who have significantly different ages of onset then there is a possibility of discovering the specific impetus that causes an earlier age of onset and a higher recurrence of depressive episodes. There are so many factors like this that influence the severity of a major depressive case that we must realize genetics is only one component. It seems that genetics is one important component, but one that is also easily affected by other factors as we see from all the different causes of variability in genome scan results.

On the same note as the issue with the age of onset, the stage of development may impact the genetic influence of certain genes related to MDD. As we know, parts of the brain are still developing into adulthood. These regions primarily include the frontal lobe and the cerebellum. Due to this continued development, it is likely that an individual’s genetic makeup and susceptibility to things like MDD is also changing. I would propose that at different stages of development, the genes (those that had significant linkage in the genome scan studies discussed throughout this paper) that are said to be linked to major depression would react differently to something triggering a depressive episode. Perhaps at some stages of development, a trigger would be ignored and the gene for MDD would not be activated. Another hypothesis would be that there are certain genes at specific stages of development that counteract the genes linked to major depression. If this is true, is there a time when these ‘blockers’ stop working? Furthermore, if either of these hypotheses are true and the stage of development has an effect on the onset of MDD, then if the any of these genome scan studies had a large number of participants in any one developmental stage, their data would be skewed towards that groups genetic makeup and would not represent the full population of early-onset MDD sufferers.

The severity of the participants’ cases of MDD is a further complicating factor in the study and can account for some of the inconsistencies in genome scan results. For example, if a participant had a very severe case of MDD with a large number of episodes over a long period of time, specific genes may show to have a stronger impact on their level of major depression than someone with a mild case. Perhaps it is not only the strength of the gene’s expression but a difference in the genes themselves that account for the varying severities of MDD cases. If it is a difference in the genes themselves, we can reflect back on the previous paragraph that discusses genes being different at different stages of development. When we combine the issues related to both of these factors – severity of MDD case and stage of development – the fact that genes and their expression vary over time is the most likely conclusion to draw.

An additional factor that contributes to the inconsistencies in the genome scan results is the impact of life events (family deaths, romantic problems, et cetera) on participants’ depression episodes and the recurrence of these episodes. In the studies referenced in this paper, all had a large number of participants, so this should not have been a problem because the large number or participants should have outweighed the impact of participants’ varying life events and their varying numbers of episodes.

However, something not considered was regional life events. If a large number of participants were taken from Michigan for example, a state with high unemployment rate and quickly becoming one of the poorest states in the nation, many of the participants could have experienced job loss, layoffs, or even loss of their homes. These life events are all significant enough to trigger a depressive episode and those exposed to these sorts of out-of-the-ordinary life events may also have had a greater number of depressive episodes. If a large number of participants had similar triggers for their episodes, this could have skewed the genome scan data, and specifically made genetics less of a factor. Additionally, it could have produced data inconsistent with other studies in terms of the mean number of episodes. Perhaps participants living in states like Michigan had a higher number of depressive episodes, and again made the data unrepresentative of the typical MDD case.

Genetic sex of the participants is another factor that drastically impacts the results of the genome scans. A number of the studies that I read actually had two phases of their data analysis. One was the original analysis while the second included a sex dependent analysis to account for gender differences. In the secondary analyses, sex was used as a covariate to genetic linkage. In many of the studies, after performing this secondary analysis, their data completely changed. They discovered new statistically significant chromosomal regions, and this also made the psychologists in one study question the validity of their first analysis. However, both analyses were completely valid, the results are simply applicable to different groups. Some chromosomal regions only show significant linkage with sex as a covariate and others only show significant linkage without any covariate in the analyses. For example, a chromosomal region that was shown to have significant linkage in an analysis with sex as a covariate would mean that the chromosomal region in question would have a varying impact depending on if it was a male or female with MDD. This presents a complicated problem for psychologists in deciding which information to present. However, as in the case of the GenRED study by Holmans et al, the results from both analyses were presented as significant in their discussion of their research. Although they did not go into detail about the impacts of these varying analyses, they did mention earlier in their paper that these differences could be cues to sex-specific gene effects.

Lastly, inconsistencies in the studies’ methodology could have contributed to the inconsistencies in data. While reading the studies, I discovered that while all of the genome scan studies used DSM-IV criteria to diagnose depression, most of the studies used different interview methods to diagnose their participants. Depending on how greatly the interview methods differed, this could have caused a great difference in the data for each study. If the same individual that was diagnosed with MDD in one study would not have been diagnosed with MDD in another study, there are some obvious problems. If there is not consistency in diagnosis methods, it is impossible to maintain the validity and consistency of results. Whose method of interviewing and diagnosing is correct? Whose is best? There is no way of knowing the answer to these questions from the data provided in the studies. The studies stated which interview method they used and often game some detail regarding their process of interviewing. However, they did not explain why they chose their respective interview methods.

The interview methods used by the psychologists in these genome scan studies include the Diagnostic Interview for Genetic Studies, Family Interview for Genetic Studies, brief screen for psychopathology (BSP), Composite International Diagnostic Interview (CIDI), and the Child and Adolescent Psychiatry Assessment (C-CAPA). As you can see there is a relatively diverse group of methods from only five studies. Similarly, the methods and computer programs used to analyze the data were equally diverse across studies. I’m unsure again as to which computer program is the most accurate, but with the inconsistencies in both interview method and computer program for analyses, there is clearly some room for variability in the results of the studies.

With all the complicating factors in these genome scans, it is phenomenal that any study was able to find significant data. Furthermore, it is amazing that any study was able to replicate the results – even if only partially – of any other study. This suggests that the chromosomal regions that were duplicated were significant because they were able to be replicated even with the plentitude of aforementioned complications and inconsistencies.

Although I have illuminated many of the possible causes of the inconsistencies in the genome scan results, this does not mean the genome scan results are illegitimate. It simply explains why all of the genome scan studies did not find the exact same results. Furthermore, the things I have pointed out simply suggest things that would make the studies and genome scan results more accurate. Again, it does not make the current findings invalid. As mentioned in the second paragraph, the current results that have been replicated at least once clearly have some validity. This validity would simply be stronger if those developing and performing the study had taken the aforementioned factors into account.

In all of these studies, the results of their genome scans found significant linkage to chromosomal regions. The aforementioned chromosomal regions 3q, 4q, 6p, 8p, 11q, 12q, 15q, and 18q all were replicated in at least on study of early-onset major depressive disorder. They are therefore accurate results for the chromosomal regions related to the cause of major depression. Each of the chromosomal regions mentioned has a genetic role in MDD, and all of the details outlined in this paper are explanations for why each of these chromosomal regions has a varying impact on major depression. Although I am only able to hypothesize about the causes of all the variability in the genome scan results, through research, anyone willing to further explore this disorder can investigate more closely the details of each chromosomal regions’ impact on major depression.